CHANGES OF BONE METABOLISM INDUCED BY PERIOPERATIVE ANTHRACYLINE- AND/OR TAXANE-BASED CHEMOTHERAPY FOR PRIMARY BREAST CANCER

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INTRODUCTION

Loss of bone mineral density (BMD) is among the well known sequelae of pharmacological therapy of patients pts) with primary breast cancer (PBC). Herit et al. (2006). Cancer therapy induced bone loss (CTBL) progresses more rapidly as compared to normal age-related changes of BMD and is known to be associated with the use of anthracyclines (A) in the adjuvant endocrine therapy of postmenopausal PBC pts (Body, 2010). Papponne et al. (2014). Anthracycline chemotherapy (ACh) may also lead to a deterioration of BMD but in contrast to CTBL therapy this phenomenon is by far less investigated (see for Hitte et al. (2006); Bjarnson et al. 2009). Most of these studies focused on the classical CMP-protocol which is no longer in common use. A few studies also investigated the effects of anthracycline-based regimens (CAF-CEF, on BMD of pts with PBC and found effects comparable to CPM (Bjarnson et al. 1998) on premenopausal pts. CBF following Cis is commonly interpreted as an indirect indicator. While the BMD decline in women experiencing secondary amenorrhea is generally more severe than in those retaining their ovarian function (Bjarnson et al., 2008; Body, 2010). However, it may also have direct effects on the bone, since postmenopausal BMD pts show a BMD of which is at least as high as in postmenopausal pts with secondary amenorrhea. As a matter of concern, investigations focused not only on effects of pre-existing bone metabolic alterations. These studies included patients with breast cancer and its pre- and postmenopausal BMD pts and also included diagnostic markers including both anthracyclines and/or taxanes are still pending. This retrospective study was undertaken in order to gain more insights into direct effects of anthracycline and/or taxane-based on the bone metabolism of both pre- and postmenopausal BMD pts.

METHODS

Data of 108 PBC pts (premenopausal, n=40; postmenopausal, n=68) receiving a total of 6091 chemotherapy cycles were analyzed. All pts must have been treated with at least 2 cycles of either adjuvant or neoadjuvant Cis based on anthracyclines, taxanes or both. In HER2- positive disease also received concomitant trastuzumab. Characteristics of pts included are summarized in Table 1. Pts receiving trastuzumab without Cis or a Cis in a regimen containing anthracyclines or taxanes (such as CPM) were excluded from this investigation as were pts with pre-existing bone metastases or a history of osteoporosis at the time of diagnosis. The following serum samples were analyzed: C-terminal telopeptide of type 1 collagen (CTP); Urinary osteocalcine, a marker of bone resorption, and alkaline phosphatase (BALP) as a sum marker of bone turnover. All three parameters were measured by commercial enzyme immunosorbent assays (ELISA) prior to start of Cis and after each of the following cycles for a maximum of 6. Baseline bone marker levels of pre- and postmenopausal pts were compared by student’s t-tests. Absolute and relative changes of baseline marker levels over time were evaluated by analysis of variance (ANOVA) for repeated measures. For all statistical analyses, p<0.05 indicated significance.

RESULTS

Figure 1 shows the baseline values for ICTP, P1NP, and BALP. For all parameters, premenopausal pts had higher significantly baseline levels as compared to premenopausal pts but within the normal range except for ICTP. ICTP pretreatment [p=0.007; P1NP, P=0.005; BALP, P=0.007]. Figure 2 shows the absolute changes from baseline for ICTP, P1NP, and BALP during neoadjuvant Cis for PBC. With the exception of ICTP, all changes were within the normal range of the particular parameter and did not reach statistical significance for both ICTP and BALP. In Figure 1A, P1NP, and ICTP changes were distinguished into age groups. The highest changes were completely until age 60 (p=0.004). Postmenopausal pts, however, experienced a sustained increase of both P1NP and ICTP, suggesting an earlier onset of bone metabolism changes. No such changes were observed in the premenopausal group. Nevertheless, all three bone markers versus baseline. Although starting from significantly different baseline values, all bone markers were largely comparable between pre- and postmenopausal patients and particularly impressive for P1NP.

CONCLUSIONS

Our study reports one of the first systematic evaluations of short- and long-term effects of modern anthracycline- and/or taxane-based regimens on the bone metabolism of PBC pts. Bone markers are increased in both groups. However, a difference in changes between pre- and postmenopausal pts could be observed. Absolute and relative changes of all three bone markers over time were largely comparable between pre- and postmenopausal pts. Particularly the ICTP values were higher than expected in both groups. No correlation was observed between ICTP and other bone markers. The sustained P1NP decrease in postmenopausal pts may indicate a generally impaired ability to recover from the profound pharmacological effects on bone metabolism in older pts or those having premenopausal pts received trastuzumab. Whether the observed short-term effects of modern periperaoperative chemotherapeutic effects on bone metabolism in older pts or those having premenopausal pts can be considered a general phenomenon which should also foster the individual importance of different agents and therapeutic antianosteolytic approaches such as trastuzumab or bisphosphonates.

REFERENCES